

39. A pharmaceutical composition as claimed in claim 14 for treatment of cerebral ischemia, selected from the group consisting of cerebral hippocampal ischemia; excitotoxic neuronal damage.
40. A pharmaceutical composition as claimed in claim 14 for treatment of social phobia, agoraphobia, and specific phobias

REMARKS

A copy of claims 1,2, 3, 4, 14 and 15, showing the amendments thereto is attached as an Appendix.

A new paragraph has been inserted on page 1 to set out the applications from which benefit is claimed. This application was filed prior to November 29, 2000 so that no petition is required. In any case priority claims were made on the declaration filed on this application.

On the issue raised in paragraph 7 of the action, it is pointed out that Application Serial No 09/254387 is a U.S. national stage entry of International Patent Application PCT/IB95/00437 which was filed on June 6, 1995. Since 35 USC 363 provides that such International Application has, with one exception, "the effect of a national patent application" it is submitted that the declaration properly set out the date of June 6, 1995 as the filing date of Serial No 09/254387 and that no new declaration is required.

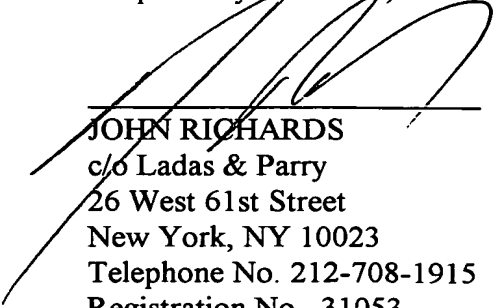
The rejections under 35 USC 112 have been met. In most cases, the corrections made are self-evident. References to Z groups and Formulae I and III have been deleted as being irrelevant to what is now claimed. So far as the use of the terms "alkyl", "alkylene", "cycloalkyl" and "cycloalkylene" including unsaturation is concerned, page 36 lines 3 to 5 make it clear that the use of these terms in the present application was in some cases intended to include unsaturated groups. In an effort to meet the examiner's concerns, where appropriate, the term "hydrocarbyl" and its derivatives has been used to replace the terms questioned by the Examiner in those definitions where the original text makes it clear that the group in question is one where reference is made to the presence of possible double or triple bonds, namely the R₁ (alkyl, alkylene, cycloalkyl, cycloalkylene and heterocycloalkyl), R₂ (alkyl, alkylene, cycloalkyl, cycloalkylene and heterocycloalkyl), R₄ (alkyl and alkylene) R₅ alkyl and alkylene), R₈ (alkyl) and any alkyl substituent of R₁₆ and R₁₇. New claim 29 is based on language that was included in claim 1 as filed as being "especial" possibilities as R₂₄ and R₂₅.

The rejection under 35 USC 102 is respectfully traversed. As noted above, the present application claims the benefit of Application Serial No 09/254387 which has a filing date of June 6, 1995. This date is prior to the publication date of WO 95/33750. Furthermore, even if this were not the case, it is pointed out that the present applicant is the same person as the author of WO/9533750 so that it is simply not possible for this document to disclose the same invention as now claimed on a date prior to the present applicant's having made such invention.

Turning now to the rejection under 35 USC 103, the issue is whether one skilled in the art would have had any reason to replace the primary amine group referred to by the examiner with a secondary one. Although there is case law that accepts that it is often obvious to make a minor modification of a known compound, particularly where the known compound has useful properties, the issue should always be fact specific. In the present case, it is not clear what the intended purpose or properties of the cited compound are. It appears to be an academic curiosity. One skilled in the art would therefore have no motivation to make the changes required. Without some motivation to make the change, the change cannot be regarded as being obvious. In re Payne, Durden and Weiden 203 USPQ 245 (CCPA 1979) at page 254. ("An obviousness rejection based on similarity of chemical structure and function entails the motivation of one skilled in the art to make the claimed compound in the expectation that compounds similar in structure will have similar properties.") The properties of the B group specified in the present claims are significantly different from primary amine groups present in the compounds of Schaefer..

In view of the foregoing it is believed that this application is now in order for allowance. An early action to this end is respectfully solicited. If the Examiner believes it would be useful to discuss this matter either personally or in a telephone interview, he is requested to let us know so that this can be arranged.

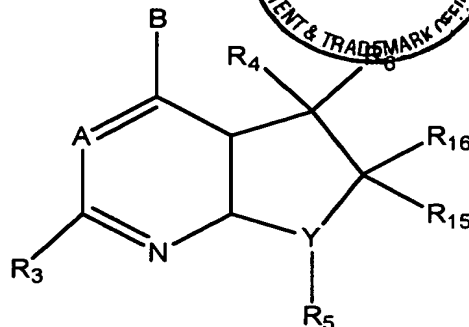
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Appendix

1(Amended) A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

A is $-\text{CR}_7$ or N;

B is $-\text{NR}_1\text{R}_2$, $-\text{CR}_1\text{R}_2\text{R}_{11}$, $-\text{C}(=\text{CR}_2\text{R}_{12})\text{R}_b$, $-\text{NHCHR}_1\text{R}_2$, $-\text{OCHR}_1\text{R}_2$, $-\text{SCHR}_1\text{R}_2$, $-\text{CHR}_2\text{OR}_1$, $-\text{CHR}_1\text{OR}_2$, $-\text{CHR}_2\text{SR}_1$, $-\text{C}(\text{S})\text{R}_2$, $-\text{C}(\text{O})\text{R}_2$, $-\text{CHR}_2\text{NR}_1\text{R}_2$, $-\text{CHR}_1\text{NHR}_2$, $-\text{CHR}_1\text{N}(\text{CH}_3)\text{R}_2$, or $-\text{NR}_{12}\text{NR}_1\text{R}_2$;

Y is CH or N;

~~Z is NH, O, S, $-\text{N}(\text{C}_1\text{-C}_2\text{-alkyl})$, $-\text{NC}(\text{O})\text{CF}_3$, or $-\text{C}(\text{R}_{13}\text{R}_{14})$, wherein R_{13} and R_{14} are each, independently, hydrogen, trifluoromethyl or methyl, or one of R_{13} and R_{14} is cyano and the other is hydrogen or methyl, or $-\text{C}(\text{R}_{13}\text{R}_{14})$ is a cyclopropyl group, or Z is nitrogen or CH and forms a five or six membered heterocyclic ring fused with R_5 , which ring optionally comprises two or three further hetero members selected independently from oxygen, nitrogen, NR_{12} , and $\text{S}(\text{O})_m$, and optionally comprises from one to three double bonds, and is optionally substituted with halo, $\text{C}_1\text{-C}_4\text{-alkyl}$, $-\text{O}(\text{C}_1\text{-C}_4\text{-alkyl})$, NH_2 , NHCH_3 , $\text{N}(\text{CH}_3)_2$, CF_3 , or OCF_3 , with the proviso that said ring does not contain any $-\text{S}-\text{S}-$, $-\text{S}-\text{O}-$, $-\text{N}-\text{S}-$, or $-\text{O}-\text{O}-$ bonds, and does not comprise more than two oxygen or $\text{S}(\text{O})_m$ heterologous members;~~

R_1 is $\text{C}(\text{O})\text{H}$, $\text{C}(\text{O})(\text{C}_1\text{-C}_6\text{ alkyl hydrocarbyl})$, $\text{C}(\text{O})(\text{C}_1\text{-C}_6\text{ alkylene hydrocarbylene})(\text{C}_3\text{-C}_8\text{ cycloalkyl cyclohydrocarbyl})$, $\text{C}(\text{O})(\text{C}_3\text{-C}_8\text{ cycloalkylene cyclohydrocarbylene})(\text{C}_3\text{-C}_8\text{ cycloalkyl cyclohydrocarbyl})$, $\text{C}(\text{O})(\text{C}_1\text{-C}_6\text{ alkylene hydrocarbylene})(\text{C}_4\text{-C}_8\text{ heterocycloalkyl heterocyclohydrocarbyl})$, $-\text{C}(\text{O})(\text{C}_3\text{-C}_8\text{ cycloalkylene cyclohydrocarbylene})(\text{C}_4\text{-C}_8\text{ heterocycloalkyl heterocyclohydrocarbyl})$, $\text{C}_1\text{-C}_6\text{ alkyl hydrocarbyl}$, $\text{C}_3\text{-C}_8\text{ cycloalkyl cyclohydrocarbyl}$, $\text{C}_4\text{-C}_8\text{ heterocycloalkyl heterocyclohydrocarbyl}$, $-(\text{C}_1\text{-C}_6\text{ alkylene hydrocarbylene})(\text{C}_3\text{-C}_8\text{ cycloalkyl cyclohydrocarbyl})$, $\text{C}_3\text{-C}_8\text{ cycloalkylene cyclohydrocarbylene})(\text{C}_3\text{-C}_8\text{ cycloalkyl cyclohydrocarbyl})$, $-(\text{C}_1\text{-C}_6\text{ alkylene hydrocarbylene})(\text{C}_4\text{-C}_8\text{ heterocycloalkyl heterocyclohydrocarbyl})$, $-(\text{C}_3\text{-C}_8\text{ cycloalkylene cyclohydrocarbylene})(\text{C}_4\text{-C}_8\text{ heterocycloalkyl heterocyclohydrocarbyl})$, or $-\text{O-aryl}$, or $-\text{O}(\text{C}_1\text{-C}_6\text{ alkylene hydrocarbylene})\text{-aryl}$; wherein said aryl, $\text{C}_4\text{-C}_8\text{ heterocycloalkyl heterocyclohydrocarbyl}$, $\text{C}_1\text{-C}_6\text{ alkyl hydrocarbyl}$, $\text{C}_3\text{-C}_8\text{ cycloalkyl cyclohydrocarbyl}$, $\text{C}_3\text{-C}_8$

cycloalkylene cyclohydrocarbylene, and C₁-C₆ alkylene hydrocarbylene groups may each independently be optionally substituted with from one to six fluoro and may each independently be optionally substituted with one or two substituents R₈ independently selected from the group consisting of C₁-C₄ alkyl hydrocarbyl, -C₃-C₈ cycloalkyl cyclohydrocarbyl, hydroxy, chloro, bromo, iodo, CF₃, -O-(C₁-C₆ alkyl hydrocarbyl), -O-(C₃-C₈ cycloalkyl cyclohydrocarbyl), -O-CO-(C₁-C₄ alkyl hydrocarbyl), -O-CO-NH(C₁-C₄ alkyl hydrocarbyl), -O-CO-N(R₂₄)(R₂₅), -N(R₂₄)(R₂₅), -S(C₁-C₄ alkyl hydrocarbyl), -S(C₃-C₈ cycloalkyl cyclohydrocarbyl), -N(C₁-C₄ alkyl hydrocarbyl)CO(C₁-C₄ alkyl hydrocarbyl), -NHCO(C₁-C₄ alkyl hydrocarbyl), -COO(C₁-C₄ alkyl hydrocarbyl), -CONH(C₁-C₄ alkyl hydrocarbyl), -CONC₁-C₄ alkyl hydrocarbyl(C₁-C₂ alkyl hydrocarbyl), CN, NO₂, -OSO₂(C₁-C₄ alkyl hydrocarbyl), S⁺(C₁-C₆ alkyl hydrocarbyl)(C₁-C₂ alkyl hydrocarbyl), -SO(C₁-C₄ alkyl hydrocarbyl) and -SO₂(C₁-C₄ alkyl hydrocarbyl); and wherein the C₁-C₆ alkyl hydrocarbyl, C₁-C₆ alkylene hydrocarbylene, C₃-C₈ cycloalkyl cyclohydrocarbyl, C₃-C₈ cycloalkylene cyclohydrocarbylene, and C₃-C₈ heterocycloalkyl heterocyclohydrocarbyl moieties of R₁ may optionally independently contain from one to three double or triple bonds; and wherein the C₁-C₄ alkyl hydrocarbyl moieties and C₁-C₆ alkyl hydrocarbyl moieties of R₈ can optionally independently be substituted with hydroxy, amino, C₁-C₄ alkyl, aryl, -CH₂-aryl, C₃-C₈ cycloalkyl, or -O-(C₁-C₄ alkyl), and can optionally independently be substituted with from one to six fluoro, and can optionally contain one or two double or triple bonds; and wherein each heterocycloalkyl heterocyclohydrocarbyl group of R₁ contains from one to three heteromoiety selected from oxygen, S(O)_m, nitrogen, and NR₁₂;

R₂ is hydrogen, C₁-C₁₂ alkyl hydrocarbyl, C₃-C₈ cycloalkyl cyclohydrocarbyl, C₄-C₈ heterocycloalkyl heterocyclohydrocarbyl, -(C₁-C₆ alkylene hydrocarbylene)(C₃-C₈ cycloalkyl cyclohydrocarbyl), -(C₃-C₈ cycloalkylene cyclohydrocarbylene)(C₃-C₈ cycloalkyl cyclohydrocarbyl), -(C₁-C₆ alkylene hydrocarbylene)(C₄-C₈ heterocycloalkyl heterocyclohydrocarbyl), -(C₃-C₈ cycloalkylene cyclohydrocarbylene)(C₄-C₈ heterocycloalkyl heterocyclohydrocarbyl), aryl, -(C₁-C₆ alkylene hydrocarbylene)aryl, or -(C₃-C₈ cycloalkylene cyclohydrocarbylene)(aryl); wherein each of the foregoing R₂ groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, and C₁-C₆ alkyl, wherein one of said one to three substituents can further be selected from bromo, iodo, C₁-C₆ alkoxy, -OH, -O-CO-(C₁-C₆ alkyl), -O-CO-N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -S (C₁-C₆ alkyl), -S(O)(C₁-C₆ alkyl), -S(O)₂(C₁-C₆ alkyl), S⁺(C₁-C₆ alkyl)(C₁-C₂ alkyl)I⁻, CN, and NO₂; and wherein the C₁-C₁₂ alkyl hydrocarbyl, -(C₁-C₆ alkylene hydrocarbylene), -(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene), and -(C₃-C₈ heterocycloalkyl) and cyclohydrocarbyl groups of 5 - 8 carbon atoms, cyclohydrocarbylene groups of 5 to 8 carbon atoms and heterocyclohydrocarbyl groups of 5 to 8 atoms moieties of R₂ may optionally independently contain from one to three double or triple bonds; and wherein each heterocycloalkyl

heterocyclohydrocarbyl group of R_2 contains from one to three heteromoieties selected from oxygen, $S(O)_m$, nitrogen, and NR_{12} ;

or when R_1 and R_2 are as in $-NHCHR_1R_2$, $-OCHR_1R_2$, $-SCHR_1R_2$, $-CHR_1R_2$ or $-NR_1R_2$, R_1 and R_2 of B may form a saturated 5- to 8-membered ring which may optionally contain one or two double bonds and in which one or two of the ring carbons may optionally be replaced by an oxygen, $S(O)_m$, nitrogen or NR_{12} ; and which carbocyclic ring can optionally be substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, C_1 - C_4 alkyl, fluoro, chloro, bromo, iodo, CF_3 , $-O-(C_1-C_4 \text{ alkyl})$, $-O-CO-(C_1-C_4 \text{ alkyl})$, $-O-CO-NH(C_1-C_4 \text{ alkyl})$, $-O-CO-N(C_1-C_4 \text{ alkyl})(C_1-C_2 \text{ alkyl})$, $-NH(C_1-C_4 \text{ alkyl})$, $-N(C_1-C_2 \text{ alkyl})(C_1-C_4 \text{ alkyl})$, $-S(C_1-C_4 \text{ alkyl})$, $-N(C_1-C_4 \text{ alkyl})CO(C_1-C_4 \text{ alkyl})$, $-NHCO(C_1-C_4 \text{ alkyl})$, $-COO(C_1-C_4 \text{ alkyl})$, $-CONH(C_1-C_4 \text{ alkyl})$, $-CON(C_1-C_4 \text{ alkyl})(C_1-C_2 \text{ alkyl})$, CN , NO_2 , $-OSO_2(C_1-C_4 \text{ alkyl})$, $-SO(C_1-C_4 \text{ alkyl})$, and $-SO(C_1-C_4 \text{ alkyl})$, wherein one of said one to three substituents can further be selected from phenyl;

R_3 is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF_3 , NH_2 , $NH(C_1-C_2 \text{ alkyl})$, $N(CH_3)_2$, $-NHCOCF_3$, $-NHCH_2CF_3$, $S(O)_m(C_1-C_4 \text{ alkyl})$, $CONH_2$, $-CONHCH_3$, $CON(CH_3)_2$, $-CF_3$, or CH_2OCH_3 ;

R_4 is hydrogen, C_1 - C_4 alkyl hydrocarbyl, C_3 - C_5 cycloalkyl, $-(C_1-C_4 \text{ alkylene hydrocarbylene})(C_3-C_5 \text{ cycloalkyl})$, $-(C_3-C_5 \text{ cycloalkylene})(C_3-C_6 \text{ cycloalkyl})$, cyano, fluoro, chloro, bromo, iodo, $-OR_{24}$, C_1 - C_6 alkoxy, $-O-$ cycloalkyl, $-O-(C_1-C_4 \text{ alkylene hydrocarbylene})(C_3-C_5 \text{ cycloalkyl})$, $-O-(C_3-C_5 \text{ cycloalkylene})(C_3-C_5 \text{ cycloalkyl})$, $-CH_2SC(S)O(C_1-C_4 \text{ alkyl})$, $-CH_2O^+F_3$, $-CH_2OCF_3$, CF_3 , amino, nitro, $-NR_{24}R_{25}$, $-(C_1-C_4 \text{ alkylene hydrocarbylene})-OR_{24}$, $-(C_1-C_4 \text{ alkylene hydrocarbylene})Cl$, $-(C_1-C_4 \text{ alkylene hydrocarbylene})NR_{24}R_{25}$, $-NHCOR_{24}$, $-NHCONR_{24}R_{25}$, $-C=NOR_{24}$, $-CH=NOR_{24}$, $-NHNOR_{24}R_{25}$, $-S(O)_mR_{24}$, $-C(O)R_{24}$, $-OC(O)R_{24}$, $-C(O)CN$, $-C(O)NR_{24}R_{25}$, $-C(O)NHNOR_{24}R_{25}$, and $-COOR_{24}$, wherein the alkyl hydrocarbyl and alkylene hydrocarbylene groups of R_4 may optionally independently contain one or two double or triple bonds and may optionally independently be substituted with one or two substituents R_{10} independently selected from hydroxy, amino, $-NHCOCH_3$, $-NHCOCH_2Cl$, $-NH(C_1-C_2 \text{ alkyl})$, $-N(C_1-C_2 \text{ alkyl})(C_1-C_2 \text{ alkyl})$, $-COO(C_1-C_4 \text{ alkyl})$, $-COOH$, $-CO(C_1-C_4 \text{ alkyl})$, C_1 - C_6 alkoxy, C_1 - C_3 thioalkyl, cyano and nitro, and with one to four substituents independently selected from fluoro and chloro;

R_5 is aryl or heteroaryl and is substituted with from one to four substituents R_{27} independently selected from halo, C_1 - C_{10} alkyl hydrocarbyl, $-(C_1-C_4 \text{ alkylene hydrocarbylene})(C_3-C_8 \text{ cycloalkyl})$, $-(C_1-C_4 \text{ alkylene hydrocarbylene})(C_4-C_8 \text{ heterocycloalkyl})$, $-(C_3-C_8 \text{ cycloalkyl})$, $-(C_4-C_8 \text{ heterocycloalkyl})$, $-(C_3-C_8 \text{ cycloalkylene})(C_3-C_8 \text{ cycloalkyl})$, $-(C_3-C_8 \text{ cycloalkylene})(C_4-C_8 \text{ heterocycloalkyl})$, C_1 - C_4 haloalkyl, C_1 - C_4 haloalkoxy, nitro, cyano, $-NR_{24}R_{25}$, $-NR_{24}COR_{25}$, $-NR_{24}CO_2R_{26}$, $-COR_{24}$, $-OR_{25}$, $-CONR_{24}R_{25}$, $-CO(NOR_{22})R_{25}$, $-CON(OR_{22})R_{23}$, $-CO_2R_{26}$, $-C=N(OR_{22})R_{23}$, and $-S(O)_mR_{23}$; wherein said C_1 - C_{10} alkyl, C_3 - C_8 cycloalkyl, $(C_1-C_4 \text{ alkylene})$

hydrocarbylene), (C₃-C₈ cycloalkyl), (C₃-C₈ cycloalkylene), and (C₄-C₈ heterocycloalkyl) groups can be optionally substituted with from one to three substituents independently selected from C₁-C₄ alkyl, C₃-C₈ cycloalkyl, (C₁-C₄ ~~alkylene~~ hydrocarbylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), C₁-C₄ haloalkyl, hydroxy, C₁-C₆ alkoxy, nitro halo, cyano, -NR₂₄R₂₅, -NR₂₄COR₂₅, NR₂₄CO₂R₂₆, -COR₂₄, -OR₂₅, -CONR₂₄R₂₅, CO₂R₂₆, -CO(NOR₂₂)R₂₅, and -S(O)_mR₂₃; and wherein two adjacent substituents of the R₅ group can optionally form a 5-7 membered ring, saturated or unsaturated, fused to ~~R⁵~~ R₅, which ring optionally can contain one, two, or three heterologous members independently selected from O, S(O)_m, and N, but not any -S-S-, -O-O-, -S-O-, or -N-S- bonds, and which ring is optionally substituted with C₁-C₄ alkyl, C₃-C₈ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), C₁-C₄ haloalkyl, nitro, halo, cyano -NR₂₄R₂₅, NR₂₄COR₂₅, NR₂₄CO₂R₂₆, -COR₂₄, -OR₂₅, -CONR₂₄R₂₅, CO₂R₂₆, -CO(NOR₂₆)R₂₅, or -S(O)_mR₂₃; wherein one of said one to four optional substituents R₂₇, can further be selected from -SO₂NH(C₁-C₄ alkyl), -SO₂NH(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), SO₂NH(C₃-C₈ cycloalkyl), -SO₂NH(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -SO₂N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -SO₂NH₂, -NHSO₂(C₁-C₄ alkyl), -NHSO₂(C₃-C₈ cycloalkyl), -NHSO₂(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), and -NHSO₂(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl); and wherein the ~~alkyl~~ hydrocarbyl, and ~~alkylene~~ hydrocarbylene groups of R₅ may independently optionally contain one double or triple bond; R₆ is hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, -(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), or -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), wherein said alkyl and cycloalkyl may optionally be substituted with one hydroxy, methoxy, ethoxy or fluoro group;

or R₆ and R₄ can together form an oxo (=O) group, or can be connected to form a 3-8 membered carbocyclic ring, optionally containing one to three double bonds, and optionally containing one, two, or three heterologous ring members selected from O, SO_m, N, and NR₁₂, but not containing any -O-O-, -S-O-, -S-S-, or -N-S- bonds, and further optionally substituted with C₁-C₄ ~~alkyl~~ hydrocarbyl or C₃-C₆ cycloalkyl, wherein said C₁-C₄ ~~alkyl~~ hydrocarbyl substituent may optionally contain one double or triple bond;

R₇ is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, -O(C₁-C₂ alkyl), -O(cyclopropyl), -COO(C₁-C₂ alkyl), -COO(C₃-C₈ cycloalkyl), -OCF₃, CF₃, -CH₂OH, or CH₂OCH₃;

R₁₁ is hydrogen, hydroxy, fluoro, ethoxy, or methoxy;

R₁₂ is hydrogen or C₁-C₄ alkyl;

R₁₆ and R₁₇ are each, independently, hydrogen, hydroxy, methyl, ethyl, methoxy, or ethoxy, except that R₁₆ and R₁₇ are not both methoxy or ethoxy;

or R₁₆ and R₁₇ together form an oxo (=O) group;

or R₁₆ and R₁₇ are connected to form a 3-8 membered carbocyclic ring, optionally containing one to three double bonds, and optionally containing from one to three heterologous

ring members selected from O, SO_m N, and NR₁₂, but not containing any -O-O-, -S-O-, -S-S-, or -N-S- bonds, and further optionally substituted with C₁-C₄ ~~alkyl~~ hydrocarbyl or C₃-C₆ cycloalkyl, wherein said C₁-C₄ ~~alkyl~~ hydrocarbyl substituent may optionally contain one double or triple bond; R₂₂ is independently at each occurrence selected from hydrogen, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, C₃-C₈ cycloalkyl, (C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), and (C₁-C₄ alkylene)(C₃-C₈ cycloalkyl);

R₂₂ is independently at each occurrence selected from hydrogen, C₁-C₁₄ alkyl, C₁-C₁₄ haloalkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, C₃-C₈ cycloalkyl, (C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), and (C₁-C₄ alkylene)(C₃-C₈ cycloalkyl);

R₂₃ is independently at each occurrence selected from C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₈ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), aryl, -(C₁-C₄ alkylene)aryl, piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine, and thiomorpholine;

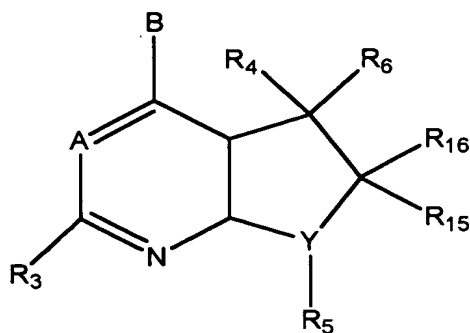
R₂₄ and R₂₅ are independently at each occurrence selected from hydrogen, -C₁-C₄ alkyl, C₁-C₄ haloalkyl, ~~especially CF₃, CHF₂, CF₂CF₃, or CH₂CF₃~~, -(C₁-C₄ alkylene)OH, -(C₁-C₄ alkylene)-O-(C₁-C₄ alkyl), -(C₁-C₄ alkylene)-O-(C₃-C₅ cycloalkyl), C₃-C₈ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -C₄-C₈ ~~heterocycloalkyl~~ heterocyclohydrocarbyl, -(C₁-C₄ alkylene)(C₄-C₈ ~~heterocycloalkyl~~ heterocyclohydrocarbyl), -(C₃-C₈ cycloalkylene)(C₄-C₈ ~~heterocycloalkyl~~ heterocyclohydrocarbyl), aryl, and -(C₁-C₄ alkylene)(aryl), wherein the -C₄-C₈ ~~heterocycloalkyl~~ heterocyclohydrocarbyl groups can each independently optionally be substituted with aryl, CH₂-aryl, or C₁-C₄ alkyl, and can optionally contain one or two double or triple bonds; or, when R₂₄ and R₂₅ are as NR₂₄R₂₅, -C(O)NR₂₄R₂₅, -(C₁-C₄ alkylene)NR₂₄R₂₅, or -NHCONR₂₄R₂₅, then NR₂₄R₂₅ may further optionally form a 4 to 8 membered heterocyclic ring optionally containing one or two further hetero members independently selected from S(O)_m, oxygen, nitrogen, and NR₁₂, and optionally containing from one to three double bonds;

R₂₆ is independently at each occurrence selected from C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₃-C₈ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), aryl, and -(C₁-C₄ alkylene)(aryl); and

wherein each m is independently zero, one, or two,

with the proviso that ~~heterocycloalkyl~~ heterocyclohydrocarbylene groups of the compound of formula ~~I, II, or III~~ do not comprise any -S-S-, -S-O-, -N-S-, or -O-O- bonds, and do not comprise more than two oxygen or S(O)_m heterologous members.

2. A compound according to claim 1 of the formula



or a pharmaceutically acceptable salt thereof, wherein

A is -CR₇ or N;

B is -NR₁R₂, -CR₁R₂R₁₁, -C(=CR₂R₁₂)R₁, -NHCHR₁R₂, -OCHR₁R₂, -SCHR₁R₂, -CHR₂OR₁₂, -CHR₂SR₁₂, -C(S)R₂ or -C(O)R₂;

Y is -CH or N;

~~Z is NH, O, S, -N(C₁-C₂ alkyl) or -C(R₁₃R₁₄), wherein R₁₃ and R₁₄ are each, independently, hydrogen, trifluoromethyl or methyl, or one of R₁₃ and R₁₄ is cyano and the other is hydrogen or methyl;~~

~~R₁ is C₁-C₆ alkyl hydrocarbyl which may optionally be substituted with one or two substituents~~
R₈ independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF₃, C₁-C₄ alkoxy, -O-CO-(C₁-C₄ a ~~alkyl hydrocarbyl~~), -O-CO-NH(C₁-C₄ ~~alkyl hydrocarbyl~~), -O-CO-N(C₁-C₄ ~~alkyl hydrocarbyl~~)(C₁-C₂ ~~alkyl hydrocarbyl~~), -NH(C₁-C₄ ~~alkyl hydrocarbyl~~), -N(C₁-C₂ alkyl)(C₁-C₄ ~~alkyl hydrocarbyl~~), -S(C₁-C₄ alkyl), -N(C₁-C₄)CO(C₁-C₄ ~~alkyl hydrocarbyl~~), -NHCO(C₁-C₄ ~~alkyl hydrocarbyl~~), -COO(C₁-C₄ ~~alkyl hydrocarbyl~~)~~alkyl hydrocarbyl~~, -CONH(C₁-C₄ ~~alkyl hydrocarbyl~~), -CON(C₁-C₄ ~~alkyl hydrocarbyl~~)(C₁-C₂ alkyl), CN, NO₂, -SO(C₁-C₄ ~~alkyl hydrocarbyl~~) and -SO₂(C₁-C₄ ~~alkyl hydrocarbyl~~), and wherein said C₁-C₆ ~~alkyl hydrocarbyl~~ and the (C₁-C₄)~~alkyl hydrocarbyl~~ moieties in the foregoing R₁ groups may optionally contain one carbon-carbon double or triple bond;

R₂ is C₁-C₁₂ ~~alkyl hydrocarbyl~~, aryl or -(C₁-C₄ ~~alkylene hydrocarbylene~~)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or -(C₁-C₆ alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said

-(C₁-C₆ alkylene)cycloalkyl having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by N-R₉ wherein R₉ is hydrogen or C₁-C₄ alkyl; and wherein each of the foregoing R₂ groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and C₁-C₄ alkyl, or with one substituent selected from bromo, iodo, C₁-C₆ alkoxy, -O-CO-(C₁-C₆ alkyl), -O-CO-N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -S(C₁-C₆ alkyl), CN, NO₂, -SO(C₁-C₄ alkyl), and -SO₂(C₁-C₄ alkyl), and wherein said C₁-C₁₂ ~~alkyl~~ hydrocarbyl and the C₁-C₄ ~~alkylene~~ hydrocarbylene moiety of said -(C₁-C₄ ~~alkylene~~ hydrocarbylene)aryl may optionally contain one carbon-carbon double or triple bond;

or -NR₁R₂ or -CR₁R₂R₁₁ may form a saturated 5- to 8-membered carbocyclic ring which may optionally contain one or two carbon-carbon double bonds and in which one or two of the ring carbons may optionally be replaced by an oxygen or sulfur atom;

R₃ is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF₃, methylthio, methylsulfonyl, CH₂OH, or CH₂OCH₃;

R₄ is hydrogen, C₁-C₄ ~~alkyl~~ hydrocarbyl, fluoro, chloro, bromo, iodo, C₁-C₄ alkoxy, trifluoromethoxy, -CH₂OCH₃, -CH₂OCH₂CH₃, -CH₂CH₂OCH₃, -CH₂OF₃, CF₃, amino, nitro, -NH(C₁-C₄ alkyl), -N(CH₃)₂, -NHCOCH₃, -NHCONHCH₃, -SO_n(C₁-C₄ ~~alkyl~~ hydrocarbyl) wherein n is 0, 1 or 2, cyano, hydroxy, -CO(C₁-C₄ ~~alkyl~~ hydrocarbyl), -CHO, cyano or -COO(C₁-C₄ alkyl) wherein said C₁-C₄ ~~alkyl~~ hydrocarbyl may optionally contain one double or triple bond and may optionally be substituted with one substituent selected from hydroxy, amino, -NHCOCH₃, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)₂, -COO(C₁-C₄ alkyl), -CO(C₁-C₄ alkyl), C₁-C₃ alkoxy, C₁-C₃ thioalkyl, fluoro, chloro, cyano and nitro;

R₅ is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, furanyl, benzofuranyl, benzothiazolyl, or indolyl, wherein each of the above groups R₅ is substituted with from one to three substituents independently selected from fluoro, chloro, C₁-C₆ alkyl, and C₁-C₆ alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, -(C₁-C₆ alkyl)O(C₁-C₆)alkyl, -NHCH₃, -N(CH₃)₂, -COOH, -COO(C₁-C₄ alkyl), -CO(C₁-C₄ alkyl), -SO₂NH(C₁-C₄ alkyl), -SO₂N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -SO₂NH₂, -NHSO₂(C₁-C₄ alkyl), -S(C₁-C₆ alkyl) and -SO₂(C₁-C₆ alkyl), and wherein the C₁-C₄ alkyl and C₁-C₆ alkyl moieties of the foregoing R₅ groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl;

R₆ is hydrogen or C₁-C₆ alkyl, wherein C₁-C₆ alkyl may optionally be substituted with one hydroxy, methoxy, ethoxy or fluoro group;

R₇ is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, -O(C₁-C₄ alkyl), -C(O)(C₁-C₄ alkyl), -C(O)O(C₁-C₄ alkyl), -OCF₃, CF₃, -CH₂OH, -CH₂OCH₃ or -CH₂OCH₂CH₃;

R₁₁ is hydrogen, hydroxy, fluoro, or methoxy;

R₁₂ is hydrogen or C₁-C₄ alkyl; and
R₁₆ and R₁₇ are each independently, hydrogen, hydroxy, ethyl, ethyl, methoxy, or ethoxy,
except that R₁₆ and R₁₇ are not both methoxy or ethoxy;
or R₁₆ and R₁₇ together form an oxo (=O) group;
or a pharmaceutically acceptable salt of such compound.

3. (Amended) A compound according to claim 2 wherein B is -NR₁R₂, -NHCHR₁R₂, -SCHR₁R₂ or -OCHR₁R₂; R₁ is C₁-C₆ ~~alkyl~~ hydrocarbyl, which may optionally be substituted with one hydroxy, fluoro, CF₃, or C₁-C₂ alkoxy group and may optionally contain one double or triple bond; and R₂ is benzyl or C₁-C₆ ~~alkyl~~ hydrocarbyl which may optionally contain one carbon-carbon double or triple bond, wherein said C₁-C₆ alkyl or the phenyl moiety of said benzyl may optionally be substituted with fluoro, CF₃, C₁-C₂ alkyl, or C₁-C₂ alkoxy.

4. (Amended) A compound according to claim 2 wherein R₁ is C₁-C₆ ~~alkyl~~ hydrocarbyl which may be substituted by fluoro, CF₃, hydroxy, C₁-C₂ alkyl or C₁-C₂ alkoxy and which may optionally contain one carbon-carbon double or triple bond.

14. (Amended) A pharmaceutical composition for the treatment of (a) a disorder or condition the treatment of which can be effected or facilitated by antagonizing CRF, ~~including but not limited to disorders induced or facilitated by CRF~~, or (b) a disorder or condition selected from inflammatory disorders ~~such as rheumatoid arthritis and osteoarthritis~~, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias, ~~including social phobia, agoraphobia, and specific phobias~~; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders ~~such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression~~, mood disorders associated with premenstrual syndrome, and postpartum depression; dysthymia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; post operative ileus; ulcer; diarrhea; stress-induced fever; human immunodeficiency virus infections; neurodegenerative diseases ~~such as Alzheimer's disease, Parkinson's disease and Huntington's disease~~; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; chemical dependencies or addictions, ~~including dependencies or addictions to alcohol, cocaine, heroin, benzodiazapines, or other drugs~~; drug or alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome

of inappropriate antidiuretic hormone; obesity; infertility; head trauma; spinal cord trauma; ischemic neuronal damage, including cerebral ischemia, ~~for example cerebral hippocampal ischemia; excitotoxic neuronal damage;~~ epilepsy; stroke; immune dysfunctions including stress induced immune dysfunctions, ~~including porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, confinement dysfunction in chicken, sheering stress in sheep, and human animal interaction stress in dogs;~~ muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multi infarct dementia; amyotrophic lateral sclerosis; hypertension; tachycardia; congestive heart failure; osteoporosis; premature birth; hypoglycemia, and Syndrome X in a mammal or bird, comprising an amount of a compound according to claim 1 that is effective in the treatment of such disorder or condition, and a pharmaceutically acceptable carrier.

15. A pharmaceutical composition according to claim 14 for the treatment of a disorder selected from inflammatory disorders ~~such as rheumatoid arthritis and osteoarthritis,~~ pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias; obsessive compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception ~~such as fibromyalgia;~~ mood disorders such as depression, ~~including major depression, single episode depression, recurrent depression, child abuse induced depression,~~ and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; human immunodeficiency virus (HIV) infections; neurodegenerative diseases ~~such as Alzheimer's disease, Parkinson's disease and Huntington's disease;~~ gastrointestinal diseases; eating disorders ~~such as anorexia and bulimia nervosa;~~ hemorrhagic stress; chemical dependencies and addictions; obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions ~~including stress induced immune dysfunctions;~~ muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multi infarct dementia; amyotrophic lateral sclerosis; and hypoglycemia in a mammal, including a human.